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EXAMINER

GHALI, ISIS A D

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1611

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

The receipt is acknowledged of applicants' amendment and request for RCE, both filed 02/23/2009.

Claims 8-11, 13, 14, 16, 20, 22-24, 29, 30, 32-38, and 40-55 are currently pending and included in the prosecution.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/23/2009 has been entered.

Specification

2. In paragraph 0123, applicant stated that "The pharmacokinetic information for loratadine is available in the literature." However, applicant did not provide any source for this information. Applicants are requested to provide on record the source of the information regarding pharmacokinetics of loratadine.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 8-11, 13, 14, 16, 20-24, 29, 30, 32-38, and 40-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,910,205 ('205) in view of applicants' admission in paragraph 0123 and US 5,968,547 ('547).

The present claims 8-11, 13, 14, 16, 47, 50 and 53 are directed to method of treating seasonal allergy or chronic urticaria comprising administering to the patient a transdermal delivery system containing loratadine, and the claims recite broad plasma levels and release rates as implied by the term "about". Claims 20-24, 29, 30, 32-38, 45, 48, 51 and 54 are directed to transdermal delivery system containing loratadine and provide broad plasma levels and release rates as

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implied by the term "about". Claims 46, 49, 52 and 55 are directed to method of treating seasonal allergy or chronic urticaria comprising administering to the patient a transdermal delivery system containing loratadine wherein the device comprises reservoir layer consisting essentially of 20-90% polymer, 0.1-30% softening agent, 0.1-20% loratadine and 0.1-30% solvent, and the claims recite broad plasma levels and release rates as implied by the term "about".

US '205 teaches a transdermal delivery system of loratadine for the treatment of allergic conditions (abstract). The system is formed of patch applied to skin for a specific period of time to permit the penetration of a desired amount of loratadine through the skin. The patch comprises a reservoir having 10-20% loratadine; 50-60% solvent; and 20-35% fatty acid esters, i.e. softening agents (col.2, lines 19-29). The patch further comprises a backing layer and a release liner (col.2, line 64; col.3, line 6). The patch will be worn from one to four days and provides a total daily dose of 0.5 to 5 mg (col.2, lines 28-34), which is from 500 μg to 5000 μg per day for one to four days. The reference disclosed patch size of 15 cm^2 , i.e. average daily released dose of 500 $\mu\text{g}/15 \text{ cm}^2/\text{day}$ to 5000 $\mu\text{g}/15 \text{ cm}^2/\text{day}$. When the dose provided by 15 cm^2 patch is divided by 15 will provide the dose per cm^2 , that is calculated 33.3 $\mu\text{g}/\text{cm}^2/\text{day}$ to 333 $\mu\text{g}/\text{cm}^2/\text{day}$, which when divided by 24 will provide the hourly dose which is calculated to be 1.4 $\mu\text{g}/\text{cm}^2/\text{hr}$ to 14 $\mu\text{g}/\text{cm}^2/\text{hr}$. The value from 1.4 $\mu\text{g}/\text{cm}^2/\text{hr}$ to 14 $\mu\text{g}/\text{cm}^2/\text{hr}$ represents the mean average release rate disclosed by the reference, and applicant claim mean average release rate from 1.8 $\mu\text{g}/\text{cm}^2/\text{hr}$ to 9.9 $\mu\text{g}/\text{cm}^2/\text{hr}$, which falls within the values disclosed by the reference. The reference disclosed that the dose may be varied depending on the size and age of the patient, and may also depend upon the severity of the condition being treated (col.3, lines 56-60). The frequency of dosage application can be once

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every 3 days to once every 7 days (col.4, lines 5-10). The claimed delivery rates are met by the reference because the claimed rates are broadened by the term “about” and inclusive of the rates disclosed by the prior art. The claimed plasma level of loratadine of the prior is are expected to be the same as those disclosed by the prior art since the prior art teaches the same daily and hourly delivery rate of loratadine for the same period of time as instantly claimed.

Additionally, the claimed release rates are determined by Valia-Chein cell, and the prior art is silent regarding the test method and the art does not appear to rely on, or teach the test method. The Patent Office is not equipped with test facilities for result testing. Hence, the instantly claimed release rates are met by the prior art.

The reference does not teach the specific delivery profile of loratadine, the specific amounts of different ingredients, or specific structure and formulation of a transdermal device including specific polymer, specific solvents and specific softening agents in the transdermal delivery system.

Applicants admit that the pharmacokinetics of loratadine is available and the release rate for a loratadine transdermal delivery system was calculated from the available data regarding the bioavailability of the oral dose.

Further, the transdermal devices suitable to deliver active agents and their structure and constituents were all known at the time of the invention.

US '547 teaches a transdermal drug delivery device for controlled delivery of drug for 3 days and maintaining the delivery for additional 2 days in accordance to the zero order kinetic of the drug (abstract). When the drug applied transdermally, it follows

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the pharmacokinetics to provide its effect over prolonged period (col.4, lines 42-67, col. 5, lines 1-8). The device comprises backing layer, polymeric reservoir and protective liner (col.20, lines 17-27). The reservoir comprising: 1-90% of polymeric material, 0.1-30% of the drug, 0.1-30% softener, and 0.1-30% of solvent (col.20, lines 55-60). The polymeric material of the reservoir is pressure sensitive adhesive and contains rubber, silicone or block-copolymers (col.18, lines 55-65). The solvents used include those contain at least one acidic group, particularly, monoesters of dicarboxylic acids, such as monomethyl glutarate and monomethyl adipate (col.20, lines 5-10). The softeners include medium chain triglycerides of the caprylic/capric acids or coconut oil, undecanol, octanol, and dodecanol (col.19, lines 58-68). The backing is laminate of polymer and aluminum foil (col.18, lines 25-30).

It is evident from the disclosure of US '547 that when the drug is included in the described transdermal device, the drug follows and is delivered according to its pharmacokinetics for period of 5 days as desired by applicants. The structure and formulation of the reservoir of the present transdermal device are identical to that of US '547. Applicants disclosed on the paragraph bridging page 23 and 24 that the pharmacokinetic information for oral loratadine is available in the literature and a release rate for a loratadine transdermal delivery system was calculated from the available data. Applicants also admit on page 24, first full paragraph that any type of transdermal delivery system may be used in accordance with the methods of the present invention so long as the desired pharmacokinetic are attained over at least 3 days to about 8 days.

Therefore, having available within hands the disclosure of US '205 that teaches loratadine delivered transdermally from formulation comprising solvent and softener, and US '547 that teaches drug delivery rate over 3-5 days following the pharmacokinetics of the drug and is attained by specific structure and formulation of a transdermal drug delivery system, along with the available pharmacokinetics of loratadine, one having ordinary skill in the art at the time of the invention would have designed transdermal drug delivery device to deliver loratadine as disclosed by US '205 and use the device disclosed by US '547 and would calculate the transdermal release rates from the available pharmacokinetic data of loratadine to achieve a transdermal delivery device having the structure and reservoir formulation comprising loratadine, polymer, softener, and solvent, wherein the device delivers loratadine at a delivery rate in accordance to its pharmacokinetics to treat patients suffering from allergic reactions with great success.

The determination of the relative release rate via an in-vitro permeation test utilizing a Valia-Chien cell is known in the art and it is not part of the claimed method of treating allergic rhinitis; or even a part of the transdermal device that provide particular plasma levels of loratadine. It is only an in-vitro diagnostic test that is expected to provide the same results obtained from two similar delivery devices tested under the same circumstances, and the recitation of this in-vitro test does not impart patentability to claims directed to method of treating allergic rhinitis or claims directed to transdermal device applied to patients to provide specific plasma levels of loratadine, i.e. in vivo use.

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Response to Arguments

6. Applicant's arguments filed 07/31/2008 have been fully considered but they are not persuasive. Applicants traverse this rejection by arguing that:

Applicants argue that the steady state concentration of loratadine of Kogan (US '205) is calculated to be approximately 0.48 ng/ml that does not overlap with the claimed steady state concentration of "about" 3 ng/ml. The cited references therefore do not teach or suggest maintaining loratadine steady state concentration of "about 3 ng/ml" as recited in independent claims 8, 20 and 46.

In response to this argument, and upon careful review to Kogan reference, it is noticed Kogan teaches mean average release rate from 1.4 $\mu\text{g}/\text{cm}^2/\text{hr}$ to 14 $\mu\text{g}/\text{cm}^2/\text{hr}$ and applicant claim mean average release rate from 1.8 $\mu\text{g}/\text{cm}^2/\text{hr}$ to 9.9 $\mu\text{g}/\text{cm}^2/\text{hr}$, which falls within the values disclosed by the reference. Therefore, the claimed release rates are met by the reference. With regard to the steady state concentration, this is not only controlled by pharmacokinetics of the drug, but also by the formulation and structure of the delivering transdermal device. In the light of Kogan disclosure that loratadine is delivered by transdermal device comprising solvent, polymer and skin softening agent, then the same plasma levels claimed by claims 8, 20 and 46 are expected. The claimed plasma level of loratadine of the prior is are expected to be the same as those disclosed by the prior art since the prior art teaches the same daily and hourly delivery rate of loratadine for the same period of time as instantly claimed. Kogan disclosed that the dose of loratadine may be varied depending on the size and age of the patient, and may also depend upon the severity of the condition being treated (col.3, lines 56-60). The frequency of dosage application can be once every 3 days to once every 7 days (col.4, lines 5-10). Therefore, one having ordinary skill in the art would

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have been able to determine the desired release rate of loratadine according to individual patient and severity of the allergic condition to be treated by manipulating the dose of loratadine and its release rate in view of doses and release rates disclosed by Kogan by manipulating the delivering formulation in view of the formulation disclosed by Reder.

Further, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Loratadine was known at the time of the invention to be administered transdermally as disclosed by Kogan. Reder taught that when the drug is included in the described transdermal device, the drug follows and is delivered according to its pharmacokinetics for period of 5 days as desired by applicants. Applicants disclosed in paragraph 0123 that the pharmacokinetic information for oral loratadine is available in the literature and a release rate for a loratadine transdermal delivery system was calculated from the available data. Applicants also admit in the same paragraph that any type of transdermal delivery system may be used in accordance with the methods of the present invention so long as the desired pharmacokinetic are attained over at least 3 days to about 8 days. Therefore, one having ordinary skill in the art at the time of the invention would have designed transdermal drug delivery device to deliver loratadine as disclosed by Kogan

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and use the device disclosed by Reder and would calculate the transdermal release rates from the available pharmacokinetic data of loratadine to achieve a transdermal delivery device having the structure and reservoir formulation comprising polymer, softener, solvent and loratadine that delivers loratadine at a delivery rate in accordance to its pharmacokinetics to treat patients suffering from allergic reactions with great success. It has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir.1992). In this case, the cited prior art in the field of applicant's endeavor since both Kogan and Reder are concerned about transdermal delivery of active agents over 3-5 days following the pharmacokinetics of the drug that is attained by specific structure and formulation of a transdermal drug delivery system, and their combination is reasonable as stated above. The invention as a whole is taught by the combination of the references; therefore, prima facie case of obviousness has been established in the meaning of USC 103 (a).

Applicants argue that the cited references do not provide a reason to change the teachings of the cited references to arrive at the presently claimed release profiles, and do not render the present claims obvious.

In response to this argument, it is established that in considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be

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expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve different problem. It is not necessary that the prior art suggest the combination or modification to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972). Kogan teaches loratadine administered transdermally and it is evident from the disclosure of Reder that when the drug is included in the described transdermal device, the drug follows and is delivered according to its pharmacokinetics for period of 5 days as desired by applicants. The structure and formulation of the reservoir of the present transdermal device are identical to that of Reder. Applicants disclosed in paragraph 0123 that the pharmacokinetic information for oral loratadine is available in the literature and a release rate for a loratadine transdermal delivery system was calculated from the available data. Applicants also admit in the same paragraph that any type of transdermal delivery system may be used in accordance with the methods of the present invention so long as the desired pharmacokinetic are attained over at least 3 days to about 8 days. At the time of the invention, one having ordinary skill in the art looking for a structure for transdermal patch for sustained release of drug and knowing the properties of the drug intended to be delivered, would have looked at Reder's patent or any other patent

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delivering drug transdermally. It has been held that "When a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR Int 'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) (quoting *Sakraida v. AG Pro, Inc.*, 425 U.S. 273,282 (1976)). "When the question is whether a patent claiming the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions."

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571) 272-0614. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should

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you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

IG

/Isis A Ghali/
Primary Examiner, Art Unit 1611